REMARKS

Claims 1-5 are presented for examination. Applicants thank the Examiner for the review of the instant application and withdrawing the objection to the title and specification, and acceptance of the copy of the sequence listing. Applicants acknowledge the Examiner's withdrawal of the rejection of Claims 1-6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The rejections of the presently pending claims are respectfully traversed.

Correction of Inventorship under 37 C.F.R. §1.48(b)

On page 5 of the previous Amendment and Response (mailed August 18, 2004), Applicants requested that several inventors listed on page 3 of the previous Amendment and Response be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. Applicants respectfully submit that this statement satisfies the requirement of 37 C.F.R. 1.48(b)(1), and note that the processing fee of $130 required under 37 C.F.R. 1.48(b)(2) was submitted with the previous response. Therefore Applicants request that the Examiner confirm that the inventors listed previously were deleted as requested.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the filing date of the present application is May 2, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. Applicants submit that for the reasons stated herein, the claimed antibodies are enabled by the disclosure of PCT/US00/23328 and have a credible, substantial, and specific utility. Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO asserts that "[g]iven the increase in amplified DNA (DNA copy number) for PRO1180" in normal kidney and rectal tumor "one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels." (Office Action at 5, emphasis added). The PTO relies

on Sen *et al.*, Pennica *et al.*, Haynes *et al.*, and Hu *et al.* for the propositions that amplification of DNA in cancer can be due to aneuploidy, that there is lack of correlation between DNA amplification and increased mRNA levels, and that polypeptide levels cannot be predicted from mRNA levels. The PTO argues that further research is required to determine the role of PRO1180 in cancer, making the asserted utility not substantial. The PTO also states that declarations submitted with Applicants' previous response are insufficient to overcome the rejection.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by

those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

*The Data in Example 18 are Data Regarding Differential mRNA Levels, **not** Gene Amplification*

Applicants begin by clarifying that the data concerning the differential expression of the PRO1180 gene presented in Example 18 relate to gene expression, **not** gene amplification. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 is reporting a measure of the *expression* of the PRO1180 gene, i.e. mRNA levels, not its *amplification*, i.e. the number of copies of PRO1180 in the genome.

Throughout the Office Action, the PTO refers to Example 18 as "amplification data." For example, the PTO states "[g]iven the increase in amplified DNA (DNA copy number) for PRO 1180...one skilled in the art would not assume that a higher expression would correlate with increased mRNA or polypeptide levels." Office Action at 5 (emphasis added). Similarly, the

PTO states that "[t]he instant specification reports data regarding amplification of individual gene..." and that "the instant specification provides no information regarding differential mRNA levels of PRO1180 .... The specification describes only gene amplification data." Office Action at 9 and 12 (emphasis added). In rejecting the declaration of Dr. Polakis, the PTO again states that "the instant specification provides no information regarding differential mRNA levels of PRO1180 .... Only gene amplification data were presented." Office Action at 13 (emphasis added).

Applicants submit that the PTO has misinterpreted the data presented in this application. Clearly, Example 18 reports data regarding differential mRNA levels, **not** gene amplification data.

As the PTO has indicated, gene amplification, i.e. an increased number of copies of a gene in the genome, can result from tissue being aneuploid. The PTO states that Sen *et al.* teaches that cancerous tissue is known to be aneuploid, and that higher amplification of a gene does not necessarily mean higher expression in the cancerous tissue. The PTO suggests that the results reported in Example 18 need "correction" for aneuploidy. Office Action at 5. The PTO also relies on Pennica *et al.* to teach that "it does not necessarily follow that an increase in gene copy number results in increased gene expression." Office Action at 15 (emphasis added). Elsewhere the PTO states that "one cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in copy number, or alternatively due to increase in transcription rates." Office Action at 11-12.

Whether or not gene amplification leads to increased gene expression is irrelevant to this particular application. Likewise, whether the differential mRNA expression of the PRO1180 gene reported in Example 18 is due to an increase or decrease in copy number, or alternatively due to an increase or decrease in transcription rates is simply not relevant. Applicants have provided reliable evidence that the PRO1180 mRNA is differentially expressed in certain tumors. Whether this differential expression is due to changes in gene copy number, transcription rates, a combination of the two, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility. It is not clear how Applicants should "correct" the reported results for aneuploidy.

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly rectal and kidney cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1180 polypeptide is expressed at least two-fold higher in rectal tumor and normal kidney than compared to normal rectum and kidney tumor, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1180 polypeptide is increased in rectal tumors compared to normal rectal tissue, it is likely that the PRO1180 polypeptide is more highly expressed in rectal tumors than normal rectum. Similarly, given Applicants' evidence that the level of mRNA for the PRO1180 polypeptide is decreased in kidney tumors compared to normal kidney tissue, it is likely that the PRO1180 polypeptide is more highly expressed in normal kidney than kidney tumors;

4. Antibodies to proteins which are differentially expressed in certain tumors are useful as diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding differential mRNA expression;

2. The PTO cites Sen *et al.* and Pennica *et al.* to support its position that gene amplification is not necessarily correlated to gene expression;

3. The PTO cites Hu *et al.* and Haynes *et al.* to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels;

4. The PTO concludes that based on the cited literature, one of skill in the art would not assume that the increase in gene amplification of PRO1180 would correlate with increased

mRNA or polypeptide levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1180 DNA supports a role for the peptide in cancerous tissue. (See Office Action at 5-6).

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, as discussed above and can be seen from Applicants' summary of their argument, Applicants submit that any lack of correlation between gene amplification and gene expression is not at issue in this application and therefore the Sen *et al.* and Pennica *et al.* references are not relevant. Third, Applicants submit that the Haynes *et al.* and Hu *et al.* references are not contrary to Applicants' arguments, and therefore are not evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1180 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's previous argument the evidence of differential expression of the gene encoding the PRO1180 polypeptide in rectal and kidney tumors is insufficient because it does not teach what the normal level of expression is, it does not indicate how high the expression level is compared to the disease tissue, it lacks statistical correlation, there is no data to compare expression in the normal and disease samples, and that because the normal and tumor samples are not from the same person, there is no possibility of direct comparison between the normal and tumor samples. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1180 gene is differentially expressed in rectal and kidney tumors.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1180 was more highly expressed in rectal tumor and normal kidney versus normal rectum and kidney tumor. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1180 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants previously submitted as Exhibit A, a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor

tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-5, offering two arguments. First, the PTO argues that "there is no evidentiary art that would corroborate for example, that 'any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue.'" Office Action at 12 (quoting first Grimaldi Declaration).

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

In addition, Applicants provide herewith as Exhibit 1 a copy of page 122 of the 2002-2003 New England Biolabs catalog. Exhibit 1 shows DNA size markers of differing lengths run on an agarose gel. The column on the left provides the mass of each marker in nanograms and the column on the right provides the length of the marker. It is apparent that the band intensity of markers having mass differences of two-fold are readily distinguishable by eye (*see e.g.*, the difference in band intensities of the 0.1kb fragment present at 61ng and the 0.5kb marker present at 124ng). Accordingly, Applicants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences.

The PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or

evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the nucleic acids of interest "can be used to differentiate tumor from normal." Together, these statements establish that there is at least a two-fold difference in expression, and that the results are reliable enough that they can be used to distinguish tumor from normal tissue.

Second, after summarizing the first Grimaldi Declaration, the PTO states that "there has been no distinction on the record in general or in the specification as filed between total nucleic acid, which includes chromosomal DNA, and mRNA." Office Action at 7. Later, the PTO states that "one cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in copy number, or alternatively due to increase in transcription rates," and that the specification does not provide any information regarding "differential mRNA levels of PRO1180," but rather "describes only gene amplification." Office Action at 11-12.

Applicant's again point out that the data in Example 18 are gene expression data, not gene amplification data. The specification and the first Grimaldi Declaration make clear that Example 18 used semi-quantitative PCR of cDNA libraries. Therefore, one of skill in the art would know that Example 18 is a measure of mRNA levels, and reflects differential PRO1180 gene expression, not gene amplification. As discussed above, the PTO cites Sen *et al.* and Pennica *et al.* for support of the argument that cancer can be aneuploid, and that gene amplification does not necessarily lead to increased gene expression. These references are irrelevant to the instant application which reports differential gene expression, not gene amplification. Therefore, these references and the PTO's arguments regarding gene amplification do not support the PTO's challenge of the sufficiency of the Example 18 data, or the first Grimaldi Declaration.

The PTO also cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for its assertion the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO states that Hu

teaches that not all genes with increased expression in cancer have a known or published role in cancer.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes that have the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of reports of a connection in the literature. But this does not mean that genes, and their corresponding proteins, with a lower level of change in expression are not important or cannot be used as molecular markers of the disease. This is demonstrated by the fact that ER-negative tumors did not show a correlation.

The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Applicants submit that a lack of known role for PRO1180 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable

change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1180 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1180 cDNA between rectal and kidney tumor tissue and the normal rectal and kidney tissue, respectively. Therefore, it follows that expression levels of the PRO1180 gene can be used to distinguish rectal and kidney tumor tissue from normal rectal and kidney tissue, respectively. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1180 polypeptide can also be used to distinguish rectal and kidney tumor tissue from normal rectal and kidney tissue, respectively. This provides utility for the claimed antibodies to the PRO1180 polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence that of differential expression of the mRNA for the PRO1180 polypeptide in rectal and kidney tumor, it is likely that the PRO1180 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)) as support for its argument that "polypeptide levels cannot be accurately predicted from mRNA levels" and that according to the results reported by Haynes, "the ratio varies from zero to 50-fold." Office Action at 5. For the reasons discussed below, Haynes is not contrary to Applicants' asserted utility.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected

because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 2 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

And even if Haynes supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit B). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit C), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in

> abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 3) and (4th ed. 2002) (submitted herewith as Exhibit 4)). Figure 9-2 of Exhibit 3 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 3 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 3 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 3 at 453 (emphasis added). Thus, as established in Exhibit 3, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 4, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 4 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 4 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 4 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for

regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 4 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 5) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 6. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 6 at 6. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 6 at 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.*

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 7, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In response to the second Grimaldi Declaration, and the Polakis Declaration, the PTO states that "it is important to note that the instant specification provides no information regarding differential mRNA levels of PRO1180.... Only gene amplification data were presented. Therefore, the declaration is insufficient to overcome the rejection of claims 1-5 ... since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptides." Office Action at 13.

Applicants again reiterate that Example 18 is information regarding differential mRNA levels of PRO1180. Thus, the PTO's rejection of the second Grimaldi Declaration and Polakis Declaration because they discuss the correlation of mRNA levels and polypeptide levels is misplaced.

The PTO also argues that further research needs to be done to determine whether the increase of decrease of PRO1180 DNA supports a role for the peptide in the cancerous tissue, and that such a role has not been suggested by the instant disclosure. *See* Office Action at 5-6.

Applicants submit that a lack of known role for PRO1180 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1180, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1180 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See,*

e.g., U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 8-11.)

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1180 mRNA is more highly expressed in rectal tumor and normal kidney compared to normal rectal tissue and kidney tumor, respectively, the PRO1180 polypeptide will also be more highly expressed in rectal tumor and normal kidney compared to normal rectal tissue and kidney tumor, respectively. This differential expression of the PRO1180 polypeptide makes antibodies to it useful as diagnostic tools for cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove

that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool. Sen *et al.* and Pennica *et al.* are irrelevant to the utility of the claimed antibodies as Example 18 reports gene expression data, not gene amplification data. Likewise, neither Hu *et al.* nor Haynes *et al.* supports the PTO's position or is contrary to Applicants' asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly rectal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1180. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1180 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1180 polypeptide is expressed at least two-fold higher in rectal tumor and normal kidney tissue compared to normal rectal tissue and kidney tumor tissue, respectively. These data are strong evidence that the PRO1180 gene and polypeptide are associated with rectal and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1180 gene and polypeptide with a specific disease. The asserted utility for antibodies to the PRO1180 polypeptide as a diagnostic tool for cancer, particularly rectal and

kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted three arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that the increase in gene amplification of PRO1180 would correlate with increased mRNA or polypeptide levels: (1) the PTO has challenged the reliability of the evidence reported in Example 18; (2) the PTO cites Sen *et al.* and Pennica *et al.* to support its position that gene amplification is not necessarily correlated to gene expression; and (3) the PTO cites Hu *et al.* and Haynes *et al.* to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1180 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. Hu *et al.* does not support the PTO's position, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.* does not address this issue, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question these declarations and supporting references.

Third, the Applicants have shown that none of the references cited by the PTO to support its position or are contrary to Applicants' asserted utility. Therefore, these references do not

satisfy the PTO's burden of offering evidence to prove that one of skill in the art would reasonably doubt the asserted utility.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1180 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1180 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §§ 102(b) and (e) – Anticipation

The PTO has maintained its rejection of Claims 1, 2, and 5 under 35 U.S.C. § 102(b) as being anticipated by Edwards *et al.* (U.S. Patent No. 6,222,029). The PTO asserts that because the application was denied the earlier filing date, Edwards is available as prior art.

For the reasons stated above, Applicants submit that the claimed antibodies have utility and are enabled, and therefore the application is entitled to a priority date of at least August 24, 2000. As the April 2001 issue date of the '029 patent is not more than a year before the August 24, 2000 priority date of the present application it is not available as prior art under 35 U.S.C. § 102(b). Applicants therefore request that the PTO reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

The PTO also maintained its rejection of Claims 1-5 under 35 U.S.C. § 102(e) as being anticipated by Edwards *et al.* (U.S. Patent 6,639,063). The PTO asserts that amino acids 139-150 of SEQ ID NO: 4227 of the '063 patent have 100% identity to an 11 amino acid fragment of SEQ ID NO: 28. The PTO states that, absent evidence to the contrary, an antibody to this sequence will bind specifically to SEQ ID NO: 28 of the instant application.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). Applicants submit that the '063 patent does not anticipate Claims 1-5 because it fails to teach each and every element of the claimed invention. As amended, Claim 1, and dependent Claims 2-5, require that the antibody specifically bind to the polypeptide of SEQ ID NO: 28.

The '063 patent discloses thousands of sequences. It does not explicitly disclose an antibody to the protein fragment consisting of amino acids amino acids 139-150 of SEQ ID NO: 4227. Where an element of a claim is not explicitly disclosed, it must be inherently disclosed to anticipate the claimed subject matter. An element is inherently disclosed only if must necessarily

follow from the disclosure. Therefore, an antibody that specifically binds to SEQ ID NO: 28 must necessarily result from the disclosure which teaches generally the production of antibodies to the disclosed proteins. If one were to immunize an animal with the polypeptide of SEQ ID NO: 4227, it does not necessarily follow that an antibody to amino acids amino acids 139-150 of SEQ ID NO: 4227 would be generated, since there is no indication that that epitope would be available. Additionally, it does not necessarily follow that an antibody to that epitope as presented in a protein of SEQ ID NO: 4227 would also specifically bind SEQ ID NO: 28. This is particularly true since SEQ ID NO: 4227 is only 22% homologous to SEQ ID NO: 28 overall.

Thus, the '063 patent does not explicitly or inherently teach an antibody which specifically binds to SEQ ID NO: 28 of the instant application. For this reason, applicants request that the PTO reconsider and withdraw the anticipation rejection under 35 U.S.C. §102(e) based on the '063 patent.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 14, 2005

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